In the Claims:

1. (canceled)

2. (currently amended) A computer-implemented method of analyzing a macromolecule for potential binding sites, ~~The method of claim 1, further~~ comprising:

(1) positioning an instance of a computer representation of a molecule or molecular fragment at a plurality of sampling sites of the macromolecule;

(2) selecting a value of B, wherein $B = \mu'/kT + ln\langle N\rangle$, where μ' is the excess chemical potential, k is Boltzmann's constant, T is the absolute temperature, and $\langle N\rangle$ is the mean number of molecules of the molecule or molecular fragment;

(3) repositioning the instances of the molecule or molecular fragment;

(4) accepting or rejecting each instance of the repositioned molecule or molecular fragment based on the Metropolis sampling criteria using the computed binding energy compared to the selected value of B;

(5) repeating steps (1) through (4) at a lesser value of B;

(6) outputting a list of unrejected instances of the molecule or molecular fragment,

wherein the molecule or molecular fragment of steps (1)-(6) is an organic fragment; and

(7) ~~(c) identifying clusters of sites that strongly bind an ORF~~ outputting a list of one or more clusters of sampling sites, wherein the clusters of sampling sites comprise closely located or superimposed sampling sites associated with the unrejected instances of the molecule or molecular fragment outputted in step (6).

3. (currently amended) The method ~~of~~ according to claim 2, further comprising:

(8) ~~(d) conducting steps (a) and (b) for each of two or more ORFs~~ repeating steps (1) through (6) for one or more additional molecules or molecular fragments, wherein said molecules or molecular fragments are organic fragments, wherein step (7) comprises ~~identifying clusters~~ outputting a list of one or more clusters of sampling sites, ~~where~~ wherein the clusters of sampling sites comprise closely located or superimposed sampling sites associated with unrejected instances of two or more distinct ~~ORFs~~ molecules or molecular fragments ~~bind~~ outputted in steps (6) and (8).

4. (currently amended) The method ~~of~~ according to claim 3, wherein ~~a cluster~~ ~~that binds~~ the clusters of sampling sites comprise closely located or superimposed sampling sites associated with unrejected instances of three or more distinct ~~ORFs~~ molecules or molecular fragments ~~is identified~~ outputted in steps (6) and (8).

5. (canceled)

6. (currently amended) A computer-implemented method of analyzing a macromolecule for potential binding sites, ~~The method of claim 3, further~~ comprising:

(1) positioning an instance of a computer representation of a molecule or molecular fragment at a plurality of sampling sites of the macromolecule;

(2) selecting a value of B, wherein $B = \mu'/kT + ln\langle N\rangle$, where μ' is the excess chemical potential, k is Boltzmann's constant, T is the absolute temperature, and $\langle N\rangle$ is the mean number of molecules of the molecule or molecular fragment;

(3) repositioning the instances of the molecule or molecular fragment;

(4) accepting or rejecting each instance of the repositioned molecule or molecular fragment based on the Metropolis sampling criteria using the computed binding energy compared to the selected value of B;

(5) repeating steps (1) through (4) at a lesser value of B;

wherein the molecule or molecular fragment of steps (1)-(5) is an organic fragment;

(6) outputting a list of unrejected instances of the molecule or molecular fragment;

(7) ~~(c) conducting, at separate values of a measure of chemical potential, two or more simulated annealing of chemical potential calculations using water as the inserted solvent; (f) comparing converged solutions from step (c) to identify locations at which water is strongly bound, thereby identifying water locations which are not candidate sites for binding ligand molecules; and (g) identifying first locations that are not water locations~~ repeating steps (1) through (5) wherein the molecule or molecular fragment is a water molecule, and outputting a list of the unrejected instances of the molecule or molecular fragment of step (6) that are not associated with unrejected instances of the water molecule; and

(8) outputting a list of one or more clusters of sampling sites, wherein the clusters of sampling sites comprise closely located or superimposed sampling sites associated with the unrejected instances of the molecule or molecular fragment outputted in step (7).

7-11. (canceled)

12. (currently amended) The method ~~of~~ according to claim ~~1~~ 2, wherein said ~~ORF~~ molecule or molecular fragment is selected from the group consisting of acetone, aldehyde, amide, ammonia, benzene, carboxylic acid, 1,4-diazine, ester, ether, formaldehyde, furan, imidazole, methane, methanol, phospho-acid, pyridine, pyrimidine, pyrrole, thiol[[,]] and thiophene.

13. (currently amended) The method ~~of~~ according to claim 3, further comprising:

(9) ~~identifying binding sites in the vicinity of said clusters which weakly bind ORFs;~~ selecting a value *B′*, wherein *B′* is a value higher than the lowest value of *B* at which steps (1) through (4) were performed;

(10) repeating steps (1) through (5) for one or more molecules or molecular fragments, wherein the value of *B* selected in step (2) is greater than or equal to *B′*; and

(11) ~~thereby identifying clusters of binding sites~~ outputting a list of

unrejected instances of the molecules or molecular fragments that are in the vicinity of a cluster of sampling sites outputted in step (7).

14. (canceled)

15. (new) The method according to claim 6, further comprising:

(9) repeating steps (1) through (6) for one or more additional molecules or molecular fragments, wherein said molecules or molecular fragments are organic fragments, wherein step (7) comprises repeating steps (1) through (5) wherein the molecule or molecular fragment is a water molecule, and outputting a list of the unrejected instances of the molecule or molecular fragment of steps (6) and (9) that are not associated with unrejected instances of the water molecule.

16. (new) The method according to claim 15, further comprising:

(10) selecting a value B', wherein B' is a value higher than the lowest value of B at which steps (1) through (4) were performed;

(11) repeating steps (1) through (5) for one or more molecules or molecular fragments, wherein the value of B selected in step (2) is greater than or equal to B'; and

(12) outputting a list of unrejected instances of the molecules or molecular fragments that are in the vicinity of a cluster of sampling sites outputted in step (8).

17. (new) The method according to claim 2, wherein step (3) comprises using a forced bias canonical probability density function.

18. (new) The method according to claim 2, wherein step (4) comprises using a grand canonical ensemble probability density function.